

Report assesses newer drugs, herbals to treat depression

You may have seen the headlines in the *New York Times* March 19, "New and Old Depression Drugs Are Found Equal." That story sparked a wild-fire of media coverage across the country about a recent systematic review, or evidence report, conducted by researchers within San Antonio's VERDICT program, and funded by the Agency for Health Care Policy and Research (AHCPR).

It's estimated that **one in five people experiences a mood disorder** in their lifetime. New antidepressants have fueled a **20% annual growth in antidepressant prescribing since 1994**. They include **29 new drugs**, spanning 9 classes. The list in the box below includes several new agents sold in the U.S. and some older agents that have been compared with the new.

This systematic review is a concise summary of the best available evidence that addressed 24 sharply defined clinical questions about newer antidepressants.

Our analysis found that newer drugs are no more efficacious than first and second generation tricyclics. The types of side effects varied between classes. We also found that St. John's wort worked better than a placebo.

But the evidence we found was not sufficient to answer many of the questions. We hope that future researchers will take note of the serious gaps in research knowledge we've identified, and will address them.

How well do new drugs work? Turn the page!

Bird's eye view of systematic review

Issues addressed:

Expert multidisciplinary panel identified many issues that included:



- ✓ Efficacy of newer drugs for the most prevalent forms of depression, and for recurrent and refractory disease
- ✓ Specific patient groups--elders, adolescents, patients with comorbidities
- ✓ Adverse effects
- ✓ Combination treatments with psychosocial therapy, other drugs

Trials reviewed:

Randomized controlled trials lasting at least 6 weeks.

Number of trials assessed:

315 met criteria; > 700 were excluded.

Outcomes assessed:

Symptomatic response, quality of life, functional status

Not included:

Cost-effectiveness of specific drugs, organization of care delivery systems.

Depression in the VA

- ✓ Among medical inpatients, nearly 15% meet diagnostic criteria for major depression.
- ✓ In VA, primary care settings, 25 to 30% of patients have significant symptoms for depression.

A sampling of drugs evaluated in report

Newer antidepressants

Selective serotonin reuptake inhibitors

Fluoxetine (Prozac)
Fluvoxamine (Luvox)
Paroxetine (Paxil)
Sertraline (Zoloft)
Citalopram (Vitalopram, Cipramil, Celexa)

Serotonin norepinephrine reuptake inhibitors

Venlafaxine (Effexor)
Mirtazapine (Remeron, Zispin)

5-HT₂ receptor antagonists

Nefazodone (Serzone)

Dopamine reuptake inhibitors

Bupropion (Wellbutrin, Zyban)

Reversible inhibitors of monoamine oxidase A (new to U.S.)

Moclobemide (Auronix, Manerix)

Older antidepressants

1st generation tricyclic antidepressants

Amitriptyline (Elavil)

2nd generation tricyclic antidepressants

Desipramine (Norpramin)
Nortriptyline (Pamelor)

Triazolopyridines

Trazodone (Desyrel)

How Should Clinicians and Health Plans Use the Evidence?

This systematic review is important because it summarizes hundreds of studies, giving readers a more precise estimate of the effects of antidepressant treatments than any single treatment trial or a traditional review. It's a task beyond the resources of most health plans or individual clinicians, but is done for

health plans and clinicians who will use the report in clinical policies and treatment decisions for patients suffering from depression. How should they use the evidence?

The data are most robust for treatment of major depression, so that will be the focus of my comments. The finding that antidepressants are beneficial is not new, but many people will be surprised by: 1) **the magnitude of effect (18% more patients improve significantly compared to those on placebo)**, 2) **the similar efficacy between drug classes**, and 3) **the small advantage in adverse effect profiles for newer drugs**. This is good news: patients and clinicians can choose from a broad array of effective drugs.

Thoughts for Clinicians

Until a breakthrough antidepressant is developed that cures patients without adverse effects, we must maximize effective use of existing agents. To do this, clinicians should consider several pragmatic issues not addressed directly by the report. First, the high dropout rates observed in these studies (30% on average) are paralleled by high rates of medication discontinuation in observed clinical practice. Interventions that improve compliance and outcomes commonly include frequent telephone or in-person follow-up to titrate dose, and

monitor symptoms and adverse effects. **Education about the following may improve adherence:** taking medication daily, expecting to wait 2 to 4 weeks for a noticeable effect, continuing medication even when feeling better, not stopping a drug without checking with your physician, and what to do if questions arise.

Interventions that improve compliance and outcomes commonly include frequent telephone or in-person follow-up to titrate dose, and monitor symptoms and adverse effects.

Studies have shown that underdosing antidepressants is common, particularly for TCAs. To replicate the benefits observed in clinical trials, physicians need to work with their patients to achieve therapeutic doses. **For some drugs, this will involve dose titration.**

Adherence is related to adverse medication effects. While dropouts due to adverse effects differed only slightly among drug classes, the **specific adverse effects differed between older and newer agents**. The consequences of specific adverse effects for individual patients (e.g., dizziness in an elderly patient with poor balance, or nausea in a patient with dyspepsia) may aid drug selection.

Thoughts for Health Plans

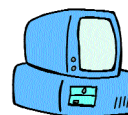
Accomplishing high quality care for depressed patients takes time and skill. The majority of health care systems, including the VA, are expanding physicians' panel sizes. Consequently, visit length may shrink and time between visits may lengthen, increasing stress on physicians trying to accomplish "best practices."

All health plans should examine systems changes to facilitate best practices. Some promising approaches are nurse specialists who offer patient education; close monitoring (often via telephone) and moving men-

tal health professionals into the primary care setting to facilitate collaborative care. Emerging data show that skilled physicians with needed resources improve outcomes for depressed patients. In the VA, we should move rapidly to implement these practices.

John W. Williams, Jr., MD
Co-author, Treatment of Depression-Newer Pharmacotherapies

How to obtain the full report



Online. A summary of the "Evidence Report on Treatment of Depression-Newer Pharmacotherapies" (AHCPR Pub. No. 99-E013) is available from AHCPR's website at: <http://www.ahcpr.gov/clinic/.htm>.

By fax. AHCPR InstantFAX. Call 301/594-2800; you must call from a facsimile machine with a telephone handset.



By mail. Hard copies will be available after July 1 from AHCPR Publications Clearinghouse, P.O. Box 8547, Silver Spring, MD 20907; telephone within the U.S.: 1/800-358-9295 and 410/381-3150 from outside the U.S.

In print. The evidence report also will be published in Volume 34, Number 4, of *Psychopharmacology Bulletin*, a publication of the National Institute of Mental Health.

Verdict Brief was prepared by Karen Stamm and Jennifer Arterburn, and Drs. Valerie Lawrence and Scott Richardson of the VA Cochrane Center @ San Antonio for the Center of Excellence in San Antonio and Charleston.

Comments can be sent to Karen Stamm, Audie L. Murphy Memorial Veterans Hospital, VA/ACOS/AC (11C6), 7400 Merton Minter Blvd., San Antonio, TX 78284. Phone: (210) 617-5300 x4266. Fax: (210) 617-5234. e-mail: kstamm@verdict.uthscsa.edu.



St. John's wort works better than placebo

Fourteen trials of at least 6 weeks duration compared St. John's wort (hypericum) to placebo or first generation tricyclic in patients with multiple depressive disorders.

St. John's wort was more effective than placebo in treating mild to moderately severe depressive disorders. **About 62% of patients receiving the herbal treatment experienced at least a 50% improvement in symptoms.** About 61% of those receiving older antidepressants experienced improvement, and about 38% of patients receiving placebo experienced 50% improvement in symptoms. adverse drug events occur significantly less frequently with St. John's wort compared to first generation tricyclics.

Evidence is lacking in many areas regarding St. John's wort:

- ✦ **Comparative efficacy to standard antidepressants**
- ✦ **Appropriate preparation and the most effective dose**
- ✦ **Effectiveness for long-term maintenance or relapse data**

Valeriana, Kava Kava: ?

Trials were found assessing the efficacy of valeriana or kava kava for treating anxiety, but not for depression.

Major Depression: Drugs vary in

SYSTEMATIC REVIEW RESULTS

We synthesized 261 trials of antidepressants in adults with major depression.

Newer agents vs. placebo and older agents

Of these, 81 studies show newer antidepressants are more effective than placebo in adults with major depression and dysthymia. About 50% of patients receiving newer antidepressants experienced at least a 50% improvement in symptoms. About 32% of those receiving placebo experienced improvement. In general, there are no significant differences in efficacy among individual newer agents or between newer and older agents.

Newer drugs are also better than placebo for depressive disorders in adults in primary care settings. Multiple agents are effective, with no evidence that any agents are significantly more effective among newer drugs, such as selective serotonin reuptake inhibitors, than first or second generation tricyclics.

The number of studies comparing different classes of newer drugs is relatively small but shows no difference in efficacy. Overall, dropouts do not differ significantly for different drugs.

Maintaining remission of major depression

For major depression, treatment with newer agents maintains remission more effectively than placebo. Efficacy for continuation-phase treatment for up to six

Dosage and cost of available on V

Drug	Generic/Brand Name
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Older Antidepressants

Amitriptyline	Generic/Elavil
Desipramine	Generic/Norpramin
Nortriptyline	Generic/Pamelor
Trazodone	Generic/Desyrel

Newer Antidepressants

Citalopram	Celexa
Fluoxetine	Prozac
Paroxetine	Paxil
Sertraline	Zoloft
Bupropion	Wellbutrin
	Wellbutrin SR
Nefazodone	Serzone
Venlafaxine	Effexor XR
Mirtazapine	Remeron

months has been shown for three SSRIs but not for other newer drugs. The evidence does not tell us if newer agents maintain remission better than older agents or psychosocial therapies. There is little data on the efficacy of newer drugs for long-term maintenance treatment beyond six months.

Recurrent depression

About 50 percent of patients with an initial depressive episode are likely to suffer a recurrence. This systematic review again found that multiple newer drugs are more effective than placebo and are as effective as older drugs in patients with recurrent depression.

Refractory depression

Few trials evaluate the benefits and risks of newer drugs for adults whose major

Effects, but not in overall efficacy

Antidepressants in the VA national formulary

Daily Dose VA 30-Day Cost

10 mg qd \$.72
20 mg qd \$3.60
30 mg qd \$1.62
30 mg tid \$5.22

10 mg qd \$26.52
20 mg qd \$35.34
30 mg qd \$31.23
40 mg qd \$35.82
40 mg tid \$45.27
60 mg bid \$41.28
60 mg bid \$27.12
60 mg qd \$35.67
80 mg qd \$34.74



depression has not responded to prior treatment. Evidence is insufficient to reliably determine response rates in such patients and whether particular antidepressant agents are more effective than others. Available trials are not long enough to evaluate appropriate duration of therapy, and none evaluate newer agents after failed psychosocial therapy.

Treating older adults

Newer drugs are better than placebo in treating major depression in older adults. No evidence suggests that any newer or older agents are significantly more effective than others.

Gaps in the evidence

- Effects of treatment on functional status and quality of life

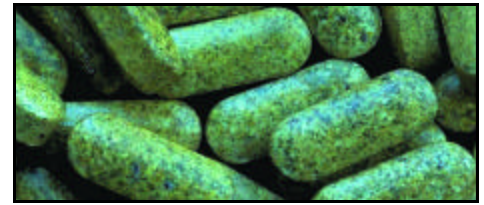
- Comparison of newer drugs vs. psychosocial therapies
- Treatment of refractory depression, particularly the efficacy of combined therapies
- Treatment of minor depression
- Treatment of patients with medical and psychiatric comorbid illness
- Long-term treatment efficacy and adverse drug events
- Effectiveness of antidepressants under usual clinical conditions without the specialized process of a randomized trial

SUMMARY IMPLICATIONS

This systematic review clearly shows newer drugs effectively treat major depression, recurrent depression, and dysthymia in mental health and in primary care settings. Because there are no significant differences in efficacy between newer drugs and first or second generation TCAs or between different classes of newer drugs, both newer and older antidepressants should be considered for therapy. Newer drugs have similar overall discontinuation rates as older drugs, but varying side effect profiles.

For clinicians: When selecting antidepressants, consider the small but statistically significant differences in adverse effects, costs, lack of data concerning relative benefits to alternative therapies (e.g., psychosocial and herbal), and individual patient preferences.

For health policy planners. Consider these factors and advocate for cost-effectiveness studies to better guide the allocation of health care dollars.



Comparative adverse drug events (ADEs)

Because of missing data and heterogeneity in methods, only comparisons between selective serotonin reuptake inhibitors (SSRIs) and first-generation tricyclics (TCA-1s) were made.

Compared to TCA-1s, SSRIs had significantly higher rates of diarrhea, nausea, insomnia, and headache. TCA had significantly higher rates of dry mouth, constipation, dizziness, blurred vision, and tremors.

Nine uncommon (<1%), but serious, ADEs were associated with SSRIs: bradycardia, bleeding, granulocytopenia, seizures, hyponatremia, hepatotoxicity, serotonin syndrome, extrapyramidal effects, and mania in unipolar depression. Bupropion was associated with seizures.

St. John's wort (hypericum) was not associated with any serious ADEs.

Although sexual dysfunction may be an important side effect of antidepressants, this outcome was reported in only 34 trials. These trials assessed and reported sexual dysfunction variably, making it impossible to compare rates of sexual dysfunction across drug classes or individual drugs.

Less than 10% of the trials explicitly reported suicide attempts and suicides.

Available randomized controlled trials provide a very limited view of ADEs associated with antidepressant use. Trials assess and report ADEs inconsistently. Trials are too short to assess long-term ADEs and too small to assess uncommon but serious ADEs.